Reviewer's report

Title: Down-regulation of Sirtuin 3 is associated with poor prognosis in hepatocellular carcinoma after resection

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Reviewer: Nadja Lehwald

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Summary:
The manuscript by Wang et al entitled “Down-regulation of Sirtuin 3 is associated with poor prognosis in hepatocellular carcinoma after resection” hypothesized that tumoral Sirt3 expression can predict the risk of recurrence and survival of HCC patients and might be useful as a future biomarker for overall survival after liver tumor resection.

The authors state that increased Sirt3 expression in tumors is strongly associated with a better prognosis in HCC patients. Conversely, down-regulated Sirt3 expression in tumor areas is found to be associated with an unfavorable clinical outcome.

In their manuscript the authors have determined sirtuin 1-7 expression with a major focus on Sirt3 in tumoral and peritumoral HCC specimens (n=342 patients) at protein level, both by immunohistochemistry and western blot. The results were further validated and correlated by univariate and multivariate analyses for recurrence and survival rate.

Major Compulsory Revisions:
The manuscript is well written and easy to understand. While the study is very interesting, it lacks rigor in investigating this very exciting new paradigm of Sirt3 as a potential biomarker to predict prognosis of HCC patients.

The authors have only presented descriptive data, but failed to explore in depth the new molecular mechanism of Sirt3 and its effects on tumor recurrence, ROS production and survival in the liver.

1. In Figure 3, the authors present western blot results of Sirt3 expression of tumoral and peritumoral specimens of 51 HCC patients. Their results in Fig. 3B demonstrate a significant reduction of Sirt3 expression in tumor samples. However, multiple patients (4, 9, 11, 13, 19, 21, 29, 31, 32,36, 39, 45, 45) show a stronger expression of Sirt3 in tumoral tissue. How do the authors explain these results? Do the western blot results correlate with disease stage and recurrence rates? Do these patients also demonstrate increased Sirt3 immunostaining?

It would be helpful if the authors could correlate the western blot results to the clinico-pathological and immunohistochemical results.

2. The authors report in the introduction and the discussion part that Sirt3 is
known to affect mitochondria and ROS production and thereby functions as a tumor inhibitor. Unfortunately, no further data is presented to support this very interesting and important hypothesis. In order to provide further mechanistic data to the manuscript, it would be very helpful if the authors could provide additional data on ROS and oxidative stress production or mitochondrial assays to further strengthen this point.

Minor Essential Revisions:
1. Space needs to be added in tumor size (table 1) “4 (1.0-21.0)“.
2. Since no data exist on tumor recurrence and death causes as mentioned on page 7 in patient profile, these data should be added to table 1 or at least stated in the text as “data not shown“.
3. Some spelling mistakes should be corrected.
4. The labeling of the x and y axis in Fig. 2 are too small.
5. In the Figure legends, Figure 1: the word “staining or expression“ is missing in the following sentence: “The micrographs showed weak…..of Sirt3 in patient I“.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests'